Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with unresectable hepatocellular carcinoma

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Background: Tislelizumab, an investigational monoclonal antibody with high affinity and binding specificity for PD-1, was engineered to minimize binding of FcγR on macrophages to help abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Two early phase studies (NCT02407990, CTR20160872) demonstrated that single-agent tislelizumab (200 mg) administered intravenously (IV) every 3 weeks (Q3W) was generally well tolerated and showed preliminary antitumor activity in patients with advanced solid tumors, including hepatocellular carcinoma (HCC).

Methods: This global Phase 2 study (NCT03419897) examined single-agent tislelizumab (200 mg IV Q3W) in patients with unresectable HCC with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) stage B/C who had received at least one prior line of systemic therapy. The primary endpoint was overall response rate by independent review committee (IRC) (ORR_{IRC}) per RECIST v1.1. Secondary endpoints included progression-free survival by IRC (PFS_{IRC}), ORR per investigator (ORR_{INV}), duration of response (DoR), overall survival (OS), and the safety/tolerability profile of tislelizumab.

Results: As of Aug 2019, 249 patients (median age 62 years) were enrolled. At study entry, 225 (90%) patients had BCLC stage C and 200 (80%) had extrahepatic spread; 111 (45%) patients had received ≥2 prior systemic therapies and 233 (94%) had received prior sorafenib. Across the study population,

confirmed ORR_{IRC} was 12.4% (95% CI: 8.6, 17.2) with 2 complete responses (CR) and 29 partial responses (PR); ORR_{INV} was 14.1% (95% CI: 10, 19.0) with 1 CR and 34 PRs. With a median study follow-up of 9.1 months, DoR_{IRC} was not reached (NR). Median OS and PFS_{IRC} were 12.4 months (95% CI: 10.8, NR) and 2.7 months (95% CI: 1.5, 2.8), respectively; the 1-year OS rate was 51.9% (95% CI: 44, 59). Number of prior lines of therapy did not impact response (1 prior line, ORR_{IRC} = 13.0% [95% CI: 7.9, 19.8]; ≥2 prior lines, ORR_{IRC} =11.7% [95% CI: 6.4, 19.2]) or survival estimates (1 prior line, median OS=13.0 months [95% CI: 10.5, NR], median PFS=2.6 months [95% CI: 1.4, 2.8]; ≥2 prior lines, median OS=11.8 months [95% CI: 10.6, NR], median PFS=2.7 months [95% CI: 1.4, 2.8]). The most common treatment-related adverse events (TRAEs) were increased AST (n=30; 12%) and ALT (n=2; 9%); increased AST (n=6; 2%) was the only grade 3–4 TRAE occurring in ≥2% of patients. Two patients had fatal AEs (infectious pneumonia, hepatic encephalopathy; n=1 each); neither was attributed to treatment by investigator.

Conclusions: Tislelizumab demonstrated durable responses and was well tolerated in patients with previously systemically treated unresectable HCC, a patient population with a continued high unmet medical need. A large, global, randomized Phase 3 study comparing tislelizumab with reference standard of care sorafenib as a first-line treatment in adult patients with unresectable HCC (NCT03412773) is currently ongoing.